POLYGENIC HYPERLIPIDEMIA INCREASES CORONARY ARTERY DISEASE RISK IN THE UK BIOBANK & FINNGEN

Pietari Ripatti, Joel T Rämö, Sanni Söderlund, Ida Surakka, Aki S Havulinna, Elisabeth Widén, Priit Palta, Nelson B Freimer, Veikko Salomaa, Matti Pirinen, Aarno Palotie, Marja-Riitta Taskinen, and Samuli Ripatti

Question: Does high polygenic burden for LDL-C or TGs identify individuals at high risk of coronary artery disease (CAD)?

Polygenic risk scores (PRS) for LDL-C and TG

Three cohorts with 440,171 individuals

The National FINRISK Study

- Finnish population cohort
- n=27 039** with lipid measures

FinnGen Project

- n=96 499** with longitudinal registry data
- 7123 CAD cases**

UK Biobank

- n=343 672** with registry data
- 16 370 CAD cases**

CAD = MACE = MI or revascularization (registry-based or self-reported)

LDL-C PRS associates with a 1.3 mmol/l difference in LDL-C and 23-63% increased CAD risk

Between the highest and lowest 5%, LDL-C differed by 1.3 mmol/l and CAD risk increased by 23-63%.

The effect was less pronounced than reported for monogenic FH (1.8 mmol/l elevation in LDL-C and 160% elevation in CAD risk).³

TG PRS associates with a 1.0 mmol/l difference in TGs and 51-57% increased CAD risk

Between the highest and lowest 5%, TG differed by 1.0 mmol/l and CAD risk increased by 51-57%.

The effect was in line with loss-of-function mutations in *APOC3* or *ANGPTL4* (0.7-0.8 mmol/l reductions in TGs and 36-53% reductions in CAD risk).⁴⁻⁵

PRSs for LDL-C & TGs are mostly independent of a CAD PRS

We constructed a PRS directly for CAD.⁶

OR for CAD between the highest and lowest 5% of the lipid PRS percentiles remained high after adjusting for the CAD PRS.

Adjusted for
Age + sex
Age + sex +
CAD PRS

Adjusted for
Age + sex
Age + sex +
CAD PRS

CONCLUSIONS

1. High polygenic burden significantly elevates LDL-C and TG levels
2. Polygenic hypercholesterolemia associates with less pronounced LDL-C & CAD risk elevation compared with monogenic FH
3. Polygenic hyperlipidemia increases CAD risk mostly independently of a PRS for CAD

References:

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